

# Prospective study of body size and risk for stroke amongst women below age 60

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**Abstract.** Lu M, Ye W, Adami H-O, Weiderpass E (Karolinska Institutet, Stockholm, Sweden; Clinical Epidemiology Unit, Qilu Hospital of Shandong University, Jinan, China; Cancer Registry of Norway, Montebello, Oslo, Norway; and Fudan University, Shanghai, China). Prospective study of body size and risk for stroke amongst women below age 60. *J Intern Med* 2006; **260**: 442–450.

The relation between obesity, particularly abdominal obesity, and risk of stroke amongst women remains unclear. In 1991–1992, a prospective study was initiated in Sweden amongst women who returned a self-administered questionnaire. Through linkage with nation-wide registries, 45 449 women, free of stroke at entry, were followed up until diagnosis of first incident stroke, death, or the end of follow-up in 2002. We estimated multivariate relative risks (RRs) with 95% confidence intervals (CIs) from Cox

proportional hazards regression models. A total of 170 incident stroke cases occurred during an average of 11 years of follow-up. The RR of stroke amongst women in the highest compared with the lowest quintile was 2.4 (95% CI 1.3–4.2; *P* for trend 0.04) for waist-to-hip ratio, 2.5 (95% CI 1.5–4.3; *P* for trend 0.01) for waist-to-height ratio and 2.3 (95% CI 1.2–4.3; *P* for trend 0.02) for waist circumference. Adjustment for hypertension and diabetes attenuated these risk estimates. In contrast, birth weight, body mass index (BMI) at age 18, BMI at entry, weight change in adulthood and adult height were not significantly associated with risk of stroke. This study provides evidence that, in contrast to BMI, several different measures of abdominal obesity are strong predictors of stroke in women.

**Keywords:** cohort study, obesity, risk, stroke.

## Introduction

Globally, most deaths are attributable to noncommunicable diseases and just over half of these result from cardiovascular diseases. Amongst the latter, stroke is the second most common cause of death and the leading cause of long-term disability worldwide. Hence, stroke represents a major public health problem as well as a heavy socioeconomic burden for society [1]. Although stroke is in part preventable through intervention against several established risk factors, the association between a high body mass index (BMI) and stroke remains controversial, with either positive [2] or null [3] associations reported. Some authors suggested, however, that high BMI may not be the most informative

measure of obesity with respect to risk of stroke [4] and myocardial infarction [5].

To this end, we aimed at investigating the relation between body mass, waist circumference, waist-to-hip ratio (WHR) and height to the risk of stroke using prospective data from the Swedish Women's Lifestyle and Health Study.

## Subjects and methods

### *Study cohort*

As described previously in detail [6–8], the Swedish Women's Lifestyle and Health Cohort Study was initiated in 1991 and 1992. A random sample of 96 000 women who were born between 1943 and

1962 (i.e. aged 30–50 years at inclusion) and were residing in the Uppsala Health Care Region (which comprises about one-sixth of the Swedish population) was drawn from the National Population Register at Statistics Sweden. Each individual is identified by an individually unique national registration number which encodes information on the date of birth. All women received a letter inviting them to participate in the study. The letter also requested that they answer a comprehensive questionnaire.

A total of 49 259 women returned completed questionnaires. In the present analysis, we excluded 13 women because they emigrated before the start of follow-up, 1834 women who reported coronary heart disease, 18 women who reported a stroke before cohort enrolment, and 1946 women with missing information on height or weight at cohort enrolment. Hence the study population in our main analyses included 45 449 subjects. For the analysis of WHR, 11 871 women who had no information on waist or hip circumference were further excluded, and therefore 33 578 subjects were included.

#### Exposure assessment

Information about anthropometric measures was based on the questionnaire administered at cohort enrolment. Women were asked about their birth weight, and the perceived body shape at age 7 compared with other girls of the same age. Based on pictograms provided in the questionnaire, they classified themselves as very thin, thin, average, fat and very fat. They were also asked about their waist and hip circumference, as well as weight at cohort enrolment in 1991–1992, weight at age 18 and their adult height (cm). BMI was calculated as weight (kg) divided by the square of the height (m). WHR was calculated as waist circumference divided by hip circumference. The quintiles of WHR were defined as Q1: <0.76, Q2: 0.76–0.799, Q3: 0.80–0.839, Q4: 0.84–0.879 and Q5:  $\geq$ 0.88. Waist-to-height ratio was calculated accordingly and defined as Q1: <0.44, Q2: 0.44–0.469, Q3: 0.47–0.499, Q4: 0.50–0.539 and Q5:  $\geq$ 0.54. The quarters of waist circumference was defined as Q1: <70, Q2: 70–79.9, Q3: 80–89.9 and Q4:  $\geq$ 90. We calculated BMI at age 18 and at study enrolment. We also created an indicator variable on the change in body shape between age 7 and adulthood with the following categories.

1 *Remained thin*: was thin/very thin at age 7 and had a BMI < 20 kg m<sup>-2</sup> at both age 18 and 1 year before enrolment;

2 *Decreased weight*: had average body shape at age 7 and had a BMI < 20 kg m<sup>-2</sup> at age 18 or 1 year before interview or was fat/very fat at age 7 and had a BMI < 25 kg m<sup>-2</sup> at age 18 or 1 year before interview;

3 *Remained at an average body weight*: had average body shape at age 7 and a BMI between 20 and 25 kg m<sup>-2</sup> at age 18 and 1 year before interview;

4 *Increased weight*: was thin/very thin at age 7 and had a BMI  $\geq$  20 kg m<sup>-2</sup> at age 18 or 1 year before interview or had average body size at age 7 and a BMI  $\geq$  25 kg m<sup>-2</sup> at age 18 or 1 year before interview; and

5 *Remained fat*: was over the average in body shape, was fat/very fat at age 7, and had a BMI  $\geq$  25 kg m<sup>-2</sup> at age 18 and/or 1 year before interview.

We further calculated changes in BMI between age 18 and entry to the study and classified this difference (BMI units) as decreased, increased up to 1.4 U, increased 1.5–4.0 U, and increased >4.0 U.

#### Follow-up

Identification of women with an incident stroke was achieved through linkage of the cohort data file to the Swedish Inpatient Register and Causes of Death Register. The individually unique national registration numbers present in the cohort data set and in other national registries in Sweden ensured unambiguous linkage. The National Board of Health and Welfare has established the nation-wide Inpatient Register to document individual hospital discharges. Each record, corresponding to one in-hospital episode, contains (i) the patient's national registration number, (ii) the date for hospital admission and discharge and (iii) up to eight discharge diagnoses coded according to the 9th version of the International Classification of Disease (ICD-9) from 1987 to 1996 and the 10th version (ICD-10) thereafter.

We considered cases in the Inpatient Register with any of the following codes in the main diagnosis: ischaemic stroke (occlusion of cerebral arteries) (ICD7: 332; ICD8: 433–434; ICD9: 434; ICD10: I63.3–I63.9), intra-cerebral haemorrhage (ICD7: 331; ICD8,9: 431; ICD10: I61) and undefined stroke (ICD7: 334; ICD8,9: 436; ICD10: I64). Because some patients might have suffered from sudden

death due to stroke without being hospitalized and thereby recorded in the Inpatient Register, we also linked our cohort to the nation-wide Causes of Death Register. If a subject was found to have different diagnoses of stroke within 28 days after index diagnosis, the subtype was defined by the latest hospital discharge. We obtained information on date of death from other diseases from the Causes of Death Register and on date of emigration out of Sweden from the Emigration Register.

### Statistical analysis

Follow-up started at the date of receipt of the returned questionnaire. Person-years was calculated from the start of follow-up to the date of first diagnosis of stroke, date of emigration or death, or end of follow-up (31 December 2002), whichever occurred first. We calculated hazard ratios as measures of relative risks (RRs) and corresponding 95% confidence intervals (CIs) using the Cox proportional hazards regression model (Proc PHREG, SAS version 8.2) [9], considering anthropometric measures as independent variables and all stroke, ischaemic stroke and haemorrhagic stroke as dependent variables. The basic regression

model included only age at entry (as a continuous variable) as covariate. Multivariable models included additionally the following covariates: educational attainment ( $\leq 9$ , 10–12,  $\geq 13$  years at school), smoking (nonsmoker, ex-smoker, current smoker with 1–9 cigarettes per day, current smoker with  $\geq 10$  cigarettes per day), alcohol intake (never drink,  $< 20$  g day<sup>-1</sup>, 20 to  $< 42$  g day<sup>-1</sup>, 42 to  $< 70$  g day<sup>-1</sup>,  $\geq 70$  g day<sup>-1</sup>), age at first child birth ( $< 21$ , 21–24,  $\geq 25$  years) and ever use of oral contraceptives (OCs) at enrolment. Further adjustment was made by including history of hypertension and diabetes mellitus in the multivariable model. Trends across increasing levels of obesity were calculated by creating a new variable from the median values for each quintile. This was then used in place of the quintiles as a single continuous variable.

The study was approved by the Data Inspection Boards in Sweden and by the regional ethics committees at Uppsala University and Karolinska Institutet.

### Results

Table 1 shows demographic characteristics and stroke risk factors by categories of body mass at

**Table 1** Baseline characteristics of study population: the Women's Lifestyle and Health Study cohort, 1991–2002

	Body mass index			
	<20	20–24.9	25–29.9	$\geq 30$
Study cohort	4521	28515	9820	2593
Age at entry ( $\pm$ SD, years)	38.2 $\pm$ 5.5	39.5 $\pm$ 5.7	40.5 $\pm$ 5.8	40.6 $\pm$ 5.8
Education ( $\pm$ SD, years)	12.9 $\pm$ 3.0	12.4 $\pm$ 3.0	11.7 $\pm$ 3.0	11.3 $\pm$ 3.0
Age at menarche ( $\pm$ SD, years)	13.3 $\pm$ 1.4	13.0 $\pm$ 1.3	12.8 $\pm$ 1.3	12.5 $\pm$ 1.4
Age at first birth ( $\pm$ SD, years)	25.2 $\pm$ 4.5	24.4 $\pm$ 4.4	23.7 $\pm$ 4.5	23.1 $\pm$ 4.4
Parity (mean $\pm$ SD)	1.7 $\pm$ 1.2	1.9 $\pm$ 1.1	2.0 $\pm$ 1.2	2.0 $\pm$ 1.3
Ever oral contraceptive use (%)	84.4	84.7	80.6	77.8
Age at first use of oral contraceptives ( $\pm$ SD, years)	19.5 $\pm$ 4.2	19.8 $\pm$ 4.3	20.1 $\pm$ 4.6	20.2 $\pm$ 4.6
Alcohol intake (g week <sup>-1</sup> )	25.0 $\pm$ 34.4	27.0 $\pm$ 33.8	25.1 $\pm$ 36.5	21.1 $\pm$ 44.5
Current smoker (%)	28.7	23.8	25.3	25.6
1–9 cigarettes/day	16.1	13.5	12.6	10.0
$\geq 10$ cigarettes/day	12.6	10.4	12.7	15.6
Pack-years <sup>a</sup> (mean $\pm$ SD)	10.5 $\pm$ 7.0	10.1 $\pm$ 6.8	11.3 $\pm$ 7.2	12.4 $\pm$ 7.7
Smoking before age 20 (%)	45.5	45.6	46.5	47.0
WHR	0.75 $\pm$ 0.07	0.77 $\pm$ 0.09	0.80 $\pm$ 0.08	0.85 $\pm$ 0.14
Waist (cm)	68.1 $\pm$ 5.1	74.2 $\pm$ 5.9	83.6 $\pm$ 7.7	97.4 $\pm$ 12.0
Hypertension (%)	5.1	7.2	12.8	22.3
Diabetes mellitus (%)	0.9	0.9	1.6	4.3
Follow-up duration ( $\pm$ SD, years)	11.0 $\pm$ 1.1	11.1 $\pm$ 0.9	11.0 $\pm$ 1.0	11.0 $\pm$ 1.2
Number of incident stroke cases	11	94	49	16
Ischaemic stroke	8	62	30	11
Haemorrhagic stroke	2	27	14	4
Incidence of all stroke per 100 000 person-years	22.1	29.8	45.2	56.2

SD, standard deviation; WHR, waist/hip circumference. <sup>a</sup>Pack-years: cigarette smoking packs per day  $\times$  years of smoking.

enrolment for the entire cohort. With increasing body mass, the mean age of the study participants was slightly higher and the attained educational level was slightly lower. Women with a BMI of 30 or higher had the largest number of cumulative pack-years of smoking, whilst the leanest women had the highest prevalence of current smokers of one to nine cigarettes per day. About 22% of women with a BMI  $\geq 30$  had hypertension diagnosed before cohort enrolment, compared with 5.1% amongst lean women with BMI  $< 20$ . The prevalence of diabetes mellitus was also markedly higher in women who were overweight or obese compared with women whose BMI was in the normal range.

After an average of 11.4 years of follow-up, 170 incident stroke cases were identified: 111 were ischaemic strokes (occlusion of cerebral arteries), 47 intra-cerebral haemorrhagic strokes and 12 undefined but acute cerebral vascular diseases. The incidence of stroke per 100 000 women years increased steeply with age from 6.2 (age 40–44) to 9.1 (45–49), 14.5 (50–54) and 55.2 (55–59). The corresponding incidence rates for ischaemic stroke were 3.1, 6.8, 8.1 and 36.5, and for haemorrhagic stroke were 0, 2.3, 5.6, and 14.8, respectively.

Table 2 shows RRs for stroke and its subtypes by self-reported birth weight, height, body mass at age 18, and body mass at enrolment. Birth weight appeared unrelated to risk of stroke, either ischaemic or haemorrhagic. We also analysed body shape at age 7, and found no associations either with ischaemic stroke or with haemorrhagic stroke (data not shown). Likewise, we found no significant associations between adult height and risk of stroke. The association between overweight (BMI over 24) at age 18 and ischaemic stroke observed in age-adjusted models was not statistically significant after multivariable adjustment for confounding factors, and largely eliminated when hypertension and diabetes mellitus – likely intermediary factors – were also added to the Cox regression model (Table 2). Compared to women with normal body mass at cohort enrolment, obese women had an excess risk of stroke, particularly ischaemic. However, this association became nonsignificant in multivariable models (Table 2). Besides the analytical models presented in Table 2 for body mass at age 18 and at cohort enrolment, we also fitted models adding an indicator variables for WHR in model 2, but the results remained basically unchanged (data not shown).

High WHR emerged as the strongest and least confounded risk factor for stroke, both ischaemic and haemorrhagic. Compared with women in the lowest quintile of WHR, women in the highest quintile had an age-adjusted RR of 3.1 (95% CI 1.7–5.4) for all strokes. This risk estimate was only slightly attenuated after controlling for other risk factors and still significant when history of hypertension and diabetes were also taken into account (Table 3). The risk of stroke increased significantly across quintiles of WHR (*P*-value for trend  $< 0.01$ ). The risk estimates were of borderline significance for ischaemic stroke in the fully adjusted model, but not for haemorrhagic stroke. Women with waist-to-height ratio over 0.54 had an about threefold excess risk for all stroke which was still highly significant after adjustment for confounders. This association was stronger for haemorrhagic than for ischaemic stroke.

Compared with lean women who had a waist circumference less than 70 cm, women with a waist  $\geq 90$  cm had increased risks for all stroke, and for the ischaemic but not the haemorrhagic subtype. The excess risk with increasing waist was slightly lower after multivariate adjustment for either history of hypertension or diabetes mellitus (data not shown), and decreased further when these two covariates were included in the regression model simultaneously (Table 3). When we added BMI at enrolment to the multivariate models presented in Table 3, the association between WHR and risk of stroke became even stronger. Compared with women in the lowest quartile, the RR for stroke amongst those in the highest quartile was 2.1 for WHR, 4.7 for waist-to-height ratio and 3.7 for waist circumference. For ischaemic stroke, the corresponding RR was 2.8, 5.6 and 5.8 respectively. The results for haemorrhagic stroke remained basically unchanged following adjustment for BMI and at enrolment. Hip circumference alone was not associated with the risk of stroke (data not shown).

Thereafter, we analysed risk of stroke in relation to body shape changes in different life periods (Table 4). We found consistent but moderate excess risks amongst women who remained fat from age 7 to 18; these risks became nonsignificant following multivariate adjustment. We found no evidence of an association between changes in BMI from age 18

**Table 2** Height, body mass index (BMI) and birth weight and the risk of stroke: the Women's Lifestyle and Health Study cohort, 1991–2002

		All stroke			Ischaemic stroke			Intracerebral haemorrhage				
RR (95% CI)		No.	Age-ad <sup>a</sup>	Model 2 <sup>c</sup>	No.	Age-ad <sup>a</sup>	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>	No.	Age-ad <sup>a</sup>	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>
<b>Birth weight (kg)</b>												
<2.5	8	0.8 (0.4–1.6)	0.8 (0.4–1.6)	0.7 (0.3–1.5)	5	0.7 (0.3–1.8)	0.7 (0.3–1.8)	0.7 (0.3–1.7)	2	0.6 (0.1–2.6)	0.6 (0.1–2.6)	0.6 (0.1–2.5)
2.5–3	34	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	22	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	13	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
>3	92	0.8 (0.6–1.0)	0.8 (0.6–1.1)	0.8 (0.6–1.1)	60	0.8 (0.5–1.1)	0.8 (0.6–1.2)	0.8 (0.6–1.2)	23	0.6 (0.3–1.1)	0.6 (0.3–1.1)	0.6 (0.4–1.1)
<i>P</i> for trends		0.6	0.7	0.5		0.6	0.7	0.5		0.9	0.9	0.9
<b>BMI at 18 years</b>												
<19	43	1.0 (0.7–1.4)	1.0 (0.7–1.4)	1.0 (0.7–1.4)	27	1.0 (0.6–1.5)	1.0 (0.6–1.5)	1.0 (0.6–1.5)	12	0.9 (0.5–1.8)	0.9 (0.5–1.8)	0.9 (0.5–1.8)
19–23.9	93	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	58	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	28	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
≥24	21	1.7 (1.1–2.8)	1.5 (0.9–2.4)	1.3 (0.8–2.1)	17	2.2 (1.3–3.8)	1.9 (1.0–3.2)	1.6 (0.9–2.8)	4	1.1 (0.4–3.2)	1.1 (0.4–3.0)	1.0 (0.3–2.8)
<i>P</i> for trends		0.05	0.1	0.2		0.02	0.07	0.2		0.7	0.7	0.8
<b>BMI at enrolment</b>												
<20	11	0.9 (0.5–1.6)	0.9 (0.5–1.6)	0.9 (0.5–1.6)	8	1.0 (0.5–2.0)	0.9 (0.4–2.0)	0.9 (0.5–2.0)	2	0.5 (0.1–2.3)	0.6 (0.1–2.4)	0.6 (0.1–2.4)
20–24.9	94	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	62	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	27	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
25–29.9	49	1.3 (1.0–1.9)	1.2 (0.9–1.7)	1.1 (0.8–1.6)	30	1.2 (0.8–1.9)	1.1 (0.7–1.7)	1.0 (0.6–1.5)	14	1.3 (0.7–2.6)	1.3 (0.7–2.5)	1.2 (0.6–2.3)
≥30	16	1.7 (1.0–2.8)	1.4 (0.8–2.4)	1.0 (0.6–1.7)	11	1.7 (0.9–3.3)	1.5 (0.8–2.8)	1.0 (0.5–1.9)	4	1.5 (0.5–4.2)	1.3 (0.5–3.9)	1.1 (0.4–3.1)
<i>P</i> for trends		0.02	0.08	0.6		0.09	0.3	0.9		0.2	0.2	0.6
<b>Height (cm)</b>												
<158	19	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	12	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	5	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
158–162.9	34	1.0 (0.6–1.8)	1.1 (0.6–1.9)	1.1 (0.6–2.0)	24	1.1 (0.6–2.3)	1.2 (0.6–2.4)	1.3 (0.7–2.6)	8	0.9 (0.3–2.8)	0.9 (0.3–2.9)	1.0 (0.3–2.9)
163–167.9	56	0.9 (0.6–1.6)	1.0 (0.6–1.7)	1.1 (0.6–1.8)	38	1.0 (0.5–1.9)	1.1 (0.6–2.1)	1.2 (0.6–2.3)	15	1.0 (0.3–2.6)	1.0 (0.4–2.7)	1.0 (0.4–2.8)
168–172.9	36	0.7 (0.4–1.3)	0.8 (0.5–1.5)	0.9 (0.5–1.6)	21	0.7 (0.3–1.4)	0.8 (0.4–1.6)	0.9 (0.4–1.8)	13	1.0 (0.4–2.8)	1.1 (0.4–3.0)	1.1 (0.4–3.2)
≥173	25	1.2 (0.7–2.2)	1.4 (0.8–2.6)	1.5 (0.8–2.7)	16	1.3 (0.6–2.7)	1.5 (0.7–3.1)	1.5 (0.7–3.3)	6	1.1 (0.3–3.7)	1.2 (0.4–4.0)	1.3 (0.4–4.1)
<i>P</i> for trends		0.8	0.7	0.6		0.6	0.9	0.8		0.8	0.7	0.6

<sup>a</sup>Adjusted for age (as a continuous variable). <sup>b</sup>Model 1 adjusted for age (as a continuous variable), smoking, alcohol intake, age at first birth (<21, <25, ≥25), years of education (≤9, ≤12, ≥13), and ever use of oral contraceptives by the time of cohort enrolment. <sup>c</sup>Model 2 adjusted for all of the variables in model 1, with additional adjustment for history of hypertension and diabetes mellitus.

**Table 3** Abdominal obesity measured by waist-to-hip ratio (WHR) and waist-to-height ratio as predictor for stroke: the Women's Lifestyle and Health Study cohort, 1991–2002

RR (95% CI)		Ischaemic stroke			Intracerebral haemorrhage			
All stroke		No.	Age-ad <sup>a</sup>	Model 2 <sup>c</sup>	No.	Age-ad <sup>a</sup>	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>
<b>Quintiles of WHR</b>								
Q1	42	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	17	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Q2	29	1.1 (0.7–1.7)	1.0 (0.6–1.6)	1.0 (0.6–2.0)	8	0.7 (0.3–1.7)	0.7 (0.3–1.6)	0.7 (0.3–1.6)
Q3	18	1.0 (0.6–1.7)	0.9 (0.5–1.5)	0.8 (0.5–1.4)	2	0.3 (0.1–1.2)	0.3 (0.1–1.1)	0.2 (0.1–1.0)
Q4	15	1.9 (1.1–3.5)	1.6 (0.9–2.9)	1.4 (0.8–2.5)	4	0.9 (0.3–2.5)	0.7 (0.2–2.0)	0.6 (0.2–1.7)
Q5	17	3.1 (1.7–5.4)	2.4 (1.3–4.2)	1.8 (1.0–3.2)	12	3.6 (1.8–7.2)	2.7 (1.4–5.5)	1.9 (0.9–3.9)
P for trends		0.003	0.04	0.1		0.002	0.02	0.06
<b>Quintiles of waist-height ratio</b>								
Q1	31	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	22	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Q2	31	1.4 (0.8–2.2)	1.3 (0.8–2.2)	1.4 (0.8–2.2)	16	1.0 (0.5–1.9)	1.0 (0.5–1.8)	1.0 (0.5–1.8)
Q3	21	1.3 (0.8–2.3)	1.3 (0.7–2.2)	1.2 (0.7–2.1)	14	1.3 (0.6–2.5)	1.2 (0.6–2.3)	1.1 (0.6–2.2)
Q4	14	1.2 (0.6–2.3)	1.1 (0.6–2.1)	1.0 (0.5–1.9)	9	1.1 (0.5–2.3)	0.9 (0.4–2.0)	0.8 (0.4–1.8)
Q5	26	3.0 (1.8–5.1)	2.5 (1.5–4.3)	1.9 (1.1–3.2)	16	2.6 (1.4–5.0)	2.1 (1.1–4.0)	1.5 (0.8–2.9)
P for trends		0.0009	0.01	0.07		0.002	0.02	0.08
<b>Quarters of waist (cm)</b>								
Q1	15	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	9	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Q2	55	1.2 (0.7–2.0)	1.2 (0.7–2.1)	1.2 (0.7–2.1)	33	1.2 (0.6–2.4)	1.2 (0.6–2.5)	1.2 (0.6–2.5)
Q3	28	1.2 (0.7–2.2)	1.2 (0.6–2.2)	1.1 (0.6–2.1)	20	1.4 (0.6–3.1)	1.4 (0.6–3.1)	1.3 (0.6–2.9)
Q4	25	2.6 (1.4–5.0)	2.3 (1.2–4.3)	1.7 (0.9–3.4)	15	2.6 (1.1–5.9)	2.2 (1.0–5.1)	1.6 (0.7–3.8)
P for trends		0.003	0.02	0.09		0.002	0.01	0.05

<sup>a</sup>Adjusted for age (as a continuous variable). <sup>b</sup>Model 1 adjusted for age (as a continuous variable), smoking, alcohol intake, age at first birth ( $\leq 21$ ,  $< 25$ ,  $\geq 25$ ), years of education ( $\leq 9$ ,  $\leq 12$ ,  $\geq 13$ ), and ever use of oral contraceptives by the time of cohort enrolment. <sup>c</sup>Model 2 adjusted for all of the variables in model 1, with additional adjustment for history of hypertension and diabetes mellitus.

**Table 4** Body shape change in different life periods and the risk of stroke: The Women Lifestyle and Health Study cohort, 1991–2002

	RR (95% CI)								
	All stroke			Ischaemic stroke			Intracerebral haemorrhage		
	No.	Age-ad <sup>a</sup>	Model <sup>b</sup>	No.	Age-ad <sup>a</sup>	Model <sup>b</sup>	No.	Age-ad <sup>a</sup>	Model <sup>b</sup>
Body shape change from 7 to 18 years to enrolment									
Remained thin	3	0.5 (0.2–1.7)	0.5 (0.2–1.8)	1	0.3 (0.04–2.2)	0.3 (0.04–2.1)	1	0.5 (0.1–4.1)	0.6 (0.1–4.6)
Decreased weight	13	1.0 (0.5–1.8)	0.9 (0.5–1.8)	10	1.2 (0.6–2.6)	1.2 (0.6–2.5)	3	0.7 (0.2–2.4)	0.7 (0.2–2.4)
Remained average	38	1.0 (ref.)	1.0 (ref.)	23	1.0 (ref.)	1.0 (ref.)	13	1.0 (ref.)	1.0 (ref.)
Increased weight	101	1.3 (0.9–1.9)	1.2 (0.8–1.7)	66	1.4 (0.9–2.2)	1.3 (0.8–2.0)	26	1.0 (0.5–2.0)	1.0 (0.5–1.9)
Remained fat	14	1.8 (1.0–3.3)	1.4 (0.8–2.7)	10	2.1 (1.0–4.4)	1.7 (0.8–3.5)	4	1.6 (0.5–4.8)	1.4 (0.4–4.3)
Missing	1			1					
<i>P</i> for trends		0.01	0.07		0.03	0.08		0.3	0.4
Adult BMI change (difference between age 18 and at enrolment)									
Decreased	18	0.9 (0.5–1.5)	0.8 (0.4–1.4)	16	1.0 (0.5–1.8)	0.9 (0.5–1.7)	2	0.6 (0.1–2.7)	0.5 (0.1–2.6)
Increased 0–1.4	22	1.0 (ref.)	1.0 (ref.)	18	1.0 (ref.)	1.0 (ref.)	3	1.0 (ref.)	1.0 (ref.)
Increased 1.5–4.0	52	0.8 (0.5–1.2)	0.8 (0.5–1.2)	26	0.5 (0.3–0.9)	0.5 (0.3–0.9)	22	1.9 (0.8–4.7)	1.9 (0.8–4.7)
Increased >4.0	65	1.1 (0.7–1.6)	0.9 (0.6–1.4)	42	0.9 (0.5–1.4)	0.8 (0.5–1.3)	17	1.7 (0.7–4.2)	1.5 (0.6–3.8)
Missing	13			9			3		
<i>P</i> for trends		0.9	0.9		0.3	0.3		0.2	0.3

BMI, body mass index. <sup>a</sup>Adjusted for age (as a continuous variable). <sup>b</sup>Model 1 adjusted for age (as a continuous variable), smoking, alcohol intake, age at first birth (<21, <25, ≥25), years of education (≤9, ≤12, ≥13), and ever use of oral contraceptives by the time of cohort at enrolment.

to cohort enrolment – either as weight loss or weight gain – and risk of ischaemic or haemorrhagic stroke (Table 4).

## Discussion

In this prospective study of Swedish women aged less than 60 years at the end of follow-up, we found that compared with women in the lowest quintile of WHR those in the highest quintile had a twofold higher risk of stroke. This association was more marked for ischaemic than for haemorrhagic stroke. Other indicators of abdominal obesity such as waist-to-height ratio and waist circumference were also positively associated with the risk of stroke. The inclusion of BMI in the statistical models made the associations stronger for all strokes and for ischaemic stroke, but did not alter risk estimates for haemorrhagic stroke. In contrast, birth weights, body size at age 7, body mass at age 18 and at cohort enrolment, adult height and changes in body size or body mass over time were not independently associated with the risk of stroke.

Our data support the theory that abdominal obesity is an independent predictor of stroke risk. In contrast, BMI, the most commonly used measurement of overweight and obesity in epidemiological studies, was not an important determinant of

risk [10–13]. As a corollary, consequences of the global burden of overweight and obesity on cardiovascular diseases, and in particular on stroke, become underestimated if only the prevalence of BMI and not the prevalence of high WHR is taken into account in epidemiological studies, as recently emphasized [5].

The strengths of our study include the prospective design and virtually complete follow-up through record linkages. Few previous studies on stroke have been conducted amongst women below age 60. The main limitation of our study is the relatively small number of stroke cases diagnosed during follow-up. In particular, the limited number of women with haemorrhagic stroke precluded conclusive assessment of aetiological heterogeneity between this outcome and ischaemic stroke. Moreover, because exposure data were self-reported at cohort enrolment, misclassification of weight may have occurred, as overweight and obese women tend to underreport their weight [14]. It is reassuring, however, that in a previous analysis of the same cohort, body mass [15] was a strong predictor of overall mortality. We excluded 11 871 women who lacked information on waist or hip circumference, due to the similarity in distribution with the study population both in risk factors and stroke incidence (data not shown). The self-assessed body size early in

life was based on pictograms: this was a crude and nonvalidated measurement, and therefore probably prone to misclassification. It serves the only purpose of giving some indication of the direction of the associations, as it is likely to have captured extremes in a body size (very thin/very fat girls compared with peers).

Vague first suggested in 1956 that atherosclerotic risk was higher in those with abdominal compared with lower body obesity [16]. BMI may be a poor indicator of obesity. In our study, contrary to WHR and other measures of abdominal obesity, BMI was not clearly associated with stroke risk in multivariate analysis. Women with the lowest BMI at cohort enrolment had the highest prevalence of current smoking, and the highest prevalence of hypertension and diabetes. These factors may have increased the risk of stroke, and therefore confound the association between BMI and stroke. Moreover, weight or BMI may have remained stable or decreased during study follow-up period, whilst adiposity may have increased [17, 18]. We and others [19] found that the measurement of central adiposity such as WHR was a better predictor of stroke than BMI.

We found no association between self-reported birth weight and risk of stroke. There are few published studies on this subject, with contradictory results. One study found that each additional kilogram of birth weight was associated with a 11% decreased risk of stroke, with the exception of macrosomic infants [20]. In another cohort of women and men from Sweden, each kilogram increase in birth weight was associated with a 41% decreased risk of haemorrhagic stroke [21]. In the study by Singhal and Lucas, stroke risk generally rose with adult BMI and dropped with high birth weight, implicating rapid weight gain as a risk factor for stroke, as suggested by the 'growth acceleration' hypothesis [22].

Abdominal obesity may increase the risk of stroke through conventional vascular risk factors. WHR is an indicator of the absolute amount of abdominal visceral fat. Intra-abdominal fat has high lipolytic activity and is less sensitive than subcutaneous adipose tissue to the inhibitory effect of insulin on lipolysis [23]. An increased abdominal adipose tissue is therefore associated with an increased supply of free fatty acids to the liver [24]. This may increase hepatic production of very low-density lipoprotein (VLDL). WHR is also positively correlated with

plasma concentration of triglycerides and of VLDL and LDL cholesterol and inversely associated with HDL cholesterol [25–27]. Some studies have shown that abdominal obesity is related not only to endothelial dysfunction, an early marker of atherosclerotic disease, but also to haemorrhological disorders such as hyperviscosity, hyperfibrinogenemia, reduced red cell deformability and erythrocyte aggregability [28, 29]. Other biological mechanisms, including increased insulin resistance, enhanced platelet activity through increasing lipid peroxidation and inflammation, may also mediate the effects of abdominal adiposity [19].

Our data demonstrate a strong association between abdominal obesity and risk of stroke in women below age 60, without excluding a modest association between BMI and stroke. Hence, we provide further evidence of the importance of considering fat distribution when evaluating association between obesity and chronic diseases. We believe that our study has public health implications, particularly for working age women. Prevention of obesity, and possibly weight reduction amongst obese persons, especially reduction in the waist circumference, may favourably alter risk factors such as blood pressure, blood sugar level and serum lipid level, which are known to be important in the development of stroke.

### Conflict of interest statement

No conflict of interest was declared.

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### References

- 1 WHO. *The World Health Report: Shaping the Future*. Geneva: WHO, 2003.

- 2 Rosengren A, Wilhelmsen L, Lappas G, Johansson S. Body mass index, coronary heart disease and stroke in Swedish women. A prospective 19-year follow-up in the BEDA study. *Eur J Cardiovasc Prev Rehabil* 2003; **10**: 443–50.
- 3 Njolstad I, Arnesen E, Lund-Larsen PG. Body height, cardiovascular risk factors, and risk of stroke in middle-aged men and women. A 14-year follow-up of the Finnmark Study. *Circulation* 1996; **94**: 2877–82.
- 4 Walker SP, Rimm EB, Ascherio A, Kawachi I, Stampfer MJ, Willett WC. Body size and fat distribution as predictors of stroke among US men. *Am J Epidemiol* 1996; **144**: 1143–50.
- 5 Yusuf S, Hawken S, Ounpuu S *et al.* Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 2005; **366**: 1640–9.
- 6 Kumle M, Weiderpass E, Braaten T, Persson I, Adami HO, Lund E. Use of oral contraceptives and breast cancer risk: the Norwegian-Swedish Women's Lifestyle and Health Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 1375–81.
- 7 Margolis KL, Mucci L, Braaten T *et al.* Physical activity in different periods of life and the risk of breast cancer: the Norwegian-Swedish Women's Lifestyle and Health cohort study. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 27–32.
- 8 Braaten T, Weiderpass E, Kumle M, Adami HO, Lund E. Education and risk of breast cancer in the Norwegian-Swedish Women's Lifestyle and Health cohort study. *Int J Cancer* 2004; **110**: 579–83.
- 9 Cox DR. Regression models and life tables. *J R Stat Soc* 1972; **B34**: 187–220.
- 10 Haheim LL, Holme I, Hjerermann I, Leren P. Risk factors of stroke incidence and mortality. A 12-year follow-up of the Oslo Study. *Stroke* 1993; **24**: 1484–9.
- 11 Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjöström L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *Br Med J (Clin Res Ed)* 1984; **289**: 1257–61.
- 12 Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Björntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *Br Med J (Clin Res Ed)* 1984; **288**: 1401–4.
- 13 Lindénstrom E, Boysen G, Nyboe J. Lifestyle factors and risk of cerebrovascular disease in women. The Copenhagen City Heart Study. *Stroke* 1993; **24**: 1468–72.
- 14 Gillum RF, Sempos CT. Ethnic variation in validity of classification of overweight and obesity using self-reported weight and height in American women and men: the Third National Health and Nutrition Examination Survey. *Nutr J* 2005; **4**: 27.
- 15 Hjartaker A, Adami HO, Lund E, Weiderpass E. Body mass index and mortality in a prospectively studied cohort of Scandinavian women: the women's lifestyle and health cohort study. *Eur J Epidemiol* 2005; **20**: 747–54.
- 16 Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. *Am J Clin Nutr* 1956; **4**: 20–34.
- 17 Crepaldi G, Belfiore F, Bosello O *et al.* Italian Consensus Conference – overweight, obesity and health. *Int J Obes* 1991; **15**: 781–90.
- 18 Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int J Obes Relat Metab Disord* 1998; **22**: 39–47.
- 19 Suk SH, Sacco RL, Boden-Albala B *et al.* Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study. *Stroke* 2003; **34**: 1586–92.
- 20 Rich-Edwards JW, Kleinman K, Michels KB *et al.* Longitudinal study of birth weight and adult body mass index in predicting risk of coronary heart disease and stroke in women. *BMJ* 2005; **330**: 1115.
- 21 Hyppönen E, Leon DA, Kenward MG, Lithell H. Prenatal growth and risk of occlusive and haemorrhagic stroke in Swedish men and women born 1915–29: historical cohort study. *BMJ* 2001; **323**: 1033–4.
- 22 Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet* 2004; **363**: 1642–5.
- 23 Keller KB, Lemberg L. Obesity and the metabolic syndrome. *Am J Crit Care* 2003; **12**: 167–70.
- 24 Iozzo P, Takala T, Oikonen V *et al.* Effect of training status on regional disposal of circulating free fatty acids in the liver and skeletal muscle during physiological hyperinsulinemia. *Diabetes Care* 2004; **27**: 2172–7.
- 25 Ghosh A, Bose K, Das Chaudhuri AB. Association of food patterns, central obesity measures and metabolic risk factors for coronary heart disease (CHD) in middle aged Bengalee Hindu men, Calcutta, India. *Asia Pac J Clin Nutr* 2003; **12**: 166–71.
- 26 Hara M, Saitou E, Iwata F, Okada T, Harada K. Waist-to-height ratio is the best predictor of cardiovascular disease risk factors in Japanese schoolchildren. *J Atheroscler Thromb* 2002; **9**: 127–32.
- 27 Silventoinen K, Jousilahti P, Vartiainen E, Tuomilehto J. Appropriateness of anthropometric obesity indicators in assessment of coronary heart disease risk among Finnish men and women. *Scand J Public Health* 2003; **31**: 283–90.
- 28 Wessel TR, Arant CB, Olson MB *et al.* Relationship of physical fitness vs body mass index with coronary artery disease and cardiovascular events in women. *JAMA* 2004; **292**: 1179–87.
- 29 Carr MC, Brunzell JD. Abdominal obesity and dyslipidemia in the metabolic syndrome: importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. *J Clin Endocrinol Metab* 2004; **89**: 2601–7.

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